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The Bottom Line

First Steps Towards Successful Post-Transplantation Therapy for Myeloid Malignancies after Allogeneic Blood Stem Cell Transplantation

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Acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) represent the most frequent indications for allogeneic blood stem cell transplantation (allo-SCT) in Europe and the United States [1]. Advances in donor selection, immunosuppression, and supportive care, as well as the introduction of reduced-toxicity conditioning, have improved outcomes and also broadened the access for more, in particular older, patients to this potentially curative treatment option [2]. Furthermore, through the use of alternative donor sources, such as haploidentical family members, the frequency of allo-SCTs, not only for myeloid disorders, will probably continue to grow [1].

Despite these developments in patient as well as in donor selection, and the advances concerning the direct transplantation phase, relapse still represents the main cause of treatment failure and the most challenging therapeutic hurdle in the post-transplantation period. Treatment options in this situation consist of palliative care, low-dose or intensive chemotherapy, as well as cellular therapies, such as donor lymphocyte infusions (DLI), and second transplantation in selected cases. However, many patients can either not tolerate intensive therapies or are refractory to those interventions [3]. Recently, based on its efficacy, manageable toxicities, and low graft-versus-host disease (GVHD) rate, the combination of the hypomethylating agent azacitidine (Aza) and DLI has proven to be a valuable alternative, either when given preemptively or as salvage therapy for overt hematologic relapse [4]. Nevertheless, 2-year survival rates after any intervention for relapse after allo-SCT rarely exceed 30%, thereby indicating an important need for improvement [3,4].

One potential approach to reduce the risk of AML or MDS relapse after allo-SCT could be maintenance or—even better—consolidation therapy. By a direct antileukemic effect, such post-transplantation treatment may be either able to directly eliminate minimal residual disease or to control disease activity until the donor immune system is sufficiently reconstituted to mediate a graft-versus-leukemia (GVL) effect. Ideally, a suitable maintenance treatment would even promote GVL reactions without increasing the risk for GVHD.

With the goal of introducing a drug carrying these properties, Pusic et al. here present the results of a prospective, dose-finding study of decitabine (DAC) after allo-SCT [5]. This DNA methyltransferase inhibitor was administered to 24 patients with high-risk AML or MDS in remission starting a median of 95 days (range, 62 to 115) after allo-SCT. According to the study design, no formal maximum-tolerated dose was reached and the major conclusion by the authors from this study is that DAC can be given safely in an outpatient setting. Still, only 9 of 22 evaluable patients were able to complete all 8 envisaged cycles, whereas 13 patients prematurely discontinued the study, including 5 because of toxicity. As a consequence, authors concluded that 10 mg/m^2, rather than the highest dose level of 15 mg/m^2 per day, for 5 days every 6 weeks may be a better tolerated dose for subsequent studies. Two-year overall survival, disease-free survival, and cumulative incidence of relapse in this study were 56%, 48%, and 28%, respectively. As this is a small, early phase, nonrandomized trial, a definitive ranking of outcome results is impossible, but this interesting study of Pusic et al. addresses some important issues in the context of relapse prevention after allo-SCT.

First, so far no post-transplantation therapy for myeloid diseases has been approved because of lack of results from well-designed, prospective, placebo-controlled randomized trials. Indeed, early-phase studies as that presented here and a number of currently ongoing trials investigating post-transplantation therapy in patients with AML or MDS

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after allo-SCT (ClinicalTrials.gov using the search terms "allogeneic" and "maintenance"), represent an essential first step to establishing innovative post-transplantation strategies to reduce the incidence of relapse after allo-SCT for patients with high-risk myeloid malignancies.

Next, a better understanding of relapse biology and how drugs such as Aza or DAC mediate their action in the post-transplantation period is definitively needed. For example, it has been shown previously that Aza can induce expansion of regulatory T cells in humans after allo-SCT, which may be the reason for a relatively low incidence of GVHD, even after DLI [6]. For DAC, similar findings have been shown in mice by the same group reporting here on the clinical trial [7]. In contrast to the results in mice and also in contrast to Aza, no effect of DAC on Tregs was found in the current study. Furthermore, although acute GVHD was mild, DAC treatment did not influence chronic GVHD [5]. This discrepancy may be related to the fact that regulatory T cells were only investigated in peripheral blood, to pharmacodynamic differences between DAC and Aza, as well as to the relatively long interval between transplantation and beginning of DAC therapy.

Finally, 11 patients developed grade III or IV neutropenia, 33% developed grade III or IV infections, and 3 patients died because of infections, highlighting the risks of post-transplantation cytotoxic treatment.

Allo-SCT is a curative therapy and many patients with high-risk myeloid malignancies have a chance to achieve long-term cure without post-transplantation therapy. It is obvious that, for some patients, DAC given after transplantation is overtreatment with potentially detrimental side effects. Thus, in the future, special attention must be paid to patient selection in terms of relapse risk.

One approach for better risk stratification could be the knowledge of the adverse prognosis of karyotype alterations, gene mutations, and their combination. For example, some studies have shown that TP53 mutations indicate a dismal prognosis for MDS patients after allo-SCT and may be able to subdivide patients with complex karyotypes with regard to their prognosis [8]. The goal is to identify a patient population with an extraordinary high relapse risk for further studies of innovative post-transplantation strategies applied in remission. In patients with an intermediate risk for relapse after allo-SCT, overtreatment should be avoided. Therefore, minimal residual disease–triggered preemptive therapy, including DLI instead of treatment in remission, may be a better strategy, as recent studies have shown that this strategy can achieve excellent outcomes.

In summary, studies such as the one of Pusic et al. represent important first steps towards successful post-transplantation therapies for patients with AML or MDS. Better understanding of disease biology, and thereby patient selection, as well as a growing number of antileukemic and immunomodulating drugs, will hopefully help to close the gap between conditioning regimen and long-term disease control by the GVL effect.

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